REMARKS

Status of the claims

Claims 1-61 are pending in the application. Claims 1-5, 7-17, 19-25, 27-36, 38-43, 45-52, and 55-61 are rejected. Claims 6,18, 26, 37, 44, 53, and 54 are objected to. Claims 1, 4, 6, 49, 51-57 are currently amended. Claims 3 and 50 are canceled herein. No new matter is added.

Claim rejection under 35 USC §112

Claim 49 stands rejected under 35 USC §112, second paragraph, as being incomplete for omitting an essential step. Applicants respectfully traverse this rejection.

The Applicants have amended the instant claim to recite the administration step. Accordingly, in view of the claim amendments presented *supra*, Applicants respectfully request that the rejection of claim 49 under 35 U.S.C. §112, second paragraph be withdrawn.

Claims 1-3, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-51 and 55-61 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the disclosure fail to provide a representative number of species to describe and enable the genus as broadly claimed.

Applicant has amended claim 1 and the dependent claims further limit elements described in the independent claim to include the description of the adjuvants being used. In view of the current amendments to the claims, one skilled in the art would reasonably conclude, that the disclosure provides adequate description of the genus and the subgenuses to enable the instant invention as claimed. Accordingly, Applicants respectfully request that the rejection of Claims 1-3, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-51 and 55-61 rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement be withdrawn.

Claim rejection under 35 USC §103

Claims 1-4, 7-8, 10-11, 13-15, 19, 32-34, 49-52 55 and 58-60 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over **Kennel** et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15:235-244) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113). Applicants respectfully traverse this rejection.

Kennel et al teach a method of treating lung cancer with alpha-particles comprising administering a pharmacological effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate. Kennel et al do not teach methods of reducing nephrotoxicity associated with the administering ^{225}Ac bound to a HEHA-MAb 210B conjugate. In fact, **Kennel et al** observe that the tumoricidal dose causes significant acute lethal radiotoxic effect as a result of decay chain daughter α emissions (page 242, 2nd column, 2nd paragraph). Decreasing the dose reduces radiotoxicity but does not have any therapeutic efficacy. Hence, **Kennel et al** anticipate the limitations of effective use of the radioisotope coupled to a targeting monoclonal antibody therapy, and speculate on various methods to retain the daughter molecules at the tumor site (page 243, 1st column, 1st paragraph). However, they do not suggest or attempt the approach of the claimed invention, which is to alter the pharmacokinetics and accelerate the excretion of the radioactive element from the body.

Although **Jones et al** disclose evaluation of dithiol agents to reduce or prevent radiotoxicity of Lead-212 or Bismuth-212 alpha radioimmunotherapy, Jones et al do not provide any data on the efficacy of their radioimmuno conjugate *in vivo* in combination with the dithiol chelating agents. Both radioisotopes evaluated by Jones et al possess limitations associated with relative short half-lives. ^{225}Ac decays into three daughter molecules with the potential radiotoxicity associated with each daughter. Although, **Jones et al** teaches that the DMPS and DMSA prevent bismuth renal uptake, it does not teach that the same would work effectively for the Ac-225 radioimmunoconjugate. In fact, **Jones** et al only teach that DMPS appears to be a suitable chelating agent as an adjuvant treatment to Bismuth or Lead-212 alpha radioimmunotherapy and that

this conclusion is based on DMPS not adversely affecting antibody immunoreactivity, being well tolerated by animals and preventing Bismuth-205/206 from localizing in tissue (Page 112, column 2, 1st Paragraph). However, no data is presented on the effects of a radioisotope immunoconjugate and its clearance. The pharmacokinetics and tissue distribution of a free Bismuth or lead-212 radioisotope, as taught by **Jones** et al do not compare to that of a ^{225}Ac radioisotope immunoconjugate, as taught by the instant invention.

All in all, **Jones** et al is a feasibility study demonstrating safety and potential use of chelating agents given in conjunction with a radioisotope. As such **Jones et al** states "DMPS has been used clinically in patients to treat heavy metal poisoning and should also be useful in radioimmunotherapy protocols."(Page 112, column 2, I[st] Paragraph). Hence, to merely suggest the use of DMPS in the context does not provide one with a reasonable expectation of success. In view of the lethal radiotoxic effect as a result of decay chain daughter α emissions observed in **Kennel et al** and use of thiol chelating agents for reducing radiotoxicity associated with Bismuth/Lead-212 in **Jones et al**, one of ordinary skill in the art would not be motivated to combine these teachings and nor would a person of ordinary skill have any reasonable expectation of success.

In contrast, the instant specification teaches specifically the reduction of renal Bi-213 activity in response to using DMSA or DMPS as chelators in combination with the ^{225}Ac labeled HuM195 in vivo (Example 5). In addition, the instant specification does not limit to using chelators alone. The instant specification teaches adjuvants, e.g., chelators, diuretics or competitive metal blockers, either individually or in combination, may be used as an adjunct chelating therapy to modify the nephrotoxicity of bismuth-213 and/or Francium-211. Furthermore, the instant specification teaches that the combination of adjuvant therapies results in cumulative effects over individual therapies, thereby allowing for larger and more effective doses of the ^{225}Ac nanogenerator to be administered resulting in doubling or more of the therapeutic index of such radioimmunotherapies (page 19, lines14-21). Thus, combining the teachings of **Kennel** and **Jones** would not teach the claimed invention. Accordingly,

Applicants respectfully request that the rejection of claims 1-4, 7-8, 10-11, 13-15, 19, 32-34, 49-52 55 and 58-60 rejected under 35 U.S.C. §103 (a) as being unpatentable over **Kennel** et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15:235-244) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113) be withdrawn.

Claims 5 and 53 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over **Kennel** et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15:235-244) and **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of **Schilcher** et al. (J. Can. Res. Clin.Oncol.1984; 107:57-60). Applicants respectfully traverse this rejection.

Kennel et al and Jones et al are discussed supra. **Schilcher et al** teach the use of diuretic agents to reduce cisplatin associated nephrotoxicity. Cisplatin is a platinum based alkylating agent which causes DNA damage in cells and is used to treat solid tumors. Cisplatin is a heavy metal which causes damage as a metal poison of the kidney cells and this is fundamentally distinct and unrelated to the damage from the actinium daughters which are found in trace amounts and cause no damage from the metal, but rather from the alpha radiation of the cells. The instant invention teaches how to decrease radiation damage from a trace metal and not metal poisoning damage. Thus, combining **Kennel et al** with **Schilcher et al** teaches away from the instant invention.

The instant invention teaches methods of reducing nephrotoxicity associated with the administration of a radioimmunoconjugate due to the production of α-emitting daughters produced during decay of the radioisotope, while **Schilcher et al** teach use of diuresis associated with cisplatin. It is standard in the art to consider hydration and diuresis for reducing cisplatin associated nephrotoxicity. The use of diuretics to clear the Francium daughter of Actinium 225 could not be anticipated by any discussion of cisplatin or any other metals as nearly nothing is known about this rare element due to its extremely short half life (5 min). Francium is not a metal but an alkali earth element. The amount of bismuth is reduced in the kidney because it is a daughter of Francium and if

Francium drops, the bismuth will therefore too. Both, **Kennel et al** and **Jones et al**, do not suggest or attempt the approach of the instant invention, which is to alter the pharmacokinetics and accelerate the excretion of the radioactive element from the body. Instead, **Kennel et al** speculate on means of retaining daughter molecules at the site of the tumor via incorporation of ^{225}Ac in fullerene molecules and internalization of ^{225}Ac by tumor cells to reduce toxicity associated with the radioimmunoconjugate (Page 243, first Paragraph). **Kennel et al** conclude that the radiologic side effects limit the effectiveness of this therapy (Page 242, 3rd paragraph). **Jones et al** is a feasibility study demonstrating safety and potential use of chelating agents given in conjunction with a radioisotope. As such **Jones et al** states "DMPS has been used clinically in patients to treat heavy metal poisoning and should also be useful in radioimmunotherapy protocols."(Page 112, column 2, I[st] Paragraph). Hence, there exists no motivation for one of ordinary skill in the art to combine the two cited references and to expect reasonable success. Accordingly, Applicants respectfully request that the rejection of Claims 5 and 53 under 35 U.S.C. 103 (a) as being unpatentable over **Kennel et al**. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15:235-244) and **Jones et al** (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of **Schilcher et al.** (J. Can. Res. Clin.Oncol.1984; 107:57-60) be withdrawn.

Claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** et al (Science 2001; 294: 1537-1540) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113). Applicants respectfully traverse this rejection.

The Examiner states that **McDevitt et al** teach a method of treating cancerous cells with alpha particles comprising administering pharmacologically effective dose of an ^{225}Ac comprising of a functionalized chelate and is effective against various types of cancers. The Examiner further states that the ^{225}Ac conjugate is a monoclonal antibody attached to a metal chelate that complexes with the 225Ac, wherein internalization of the ^{225}Ac permits the emission of alpha particles. The Examiner cites that **McDevitt et al** assess biodistribution of their

radioimmunoconjugate and report accumulation of the Bismuth-213 daughter in the kidneys as a result of the decay of the radioisotope. The Examiner states that although **McDevitt et al** does not teach administration of adjuvants such as dithiol chelate combination with the ^{225}Ac conjugate, Jones et al does teach that a problem associated with the use of ^{212}Bi and ^{212}Pb RICs is a potential of radiotoxicity as a consequence of either premature release of the metal by the chelate agent or the metabolic catabolism of the RIT releasing from the radiometal. **Jones et al** disclose the evaluation of dithiol agents for their use as adjuvant. Thus the Examiner states that if, one of ordinary skill in the art were to combine the teachings of **McDevitt et al** with **Jones et al**, a reasonable expectation of success would exist. Applicants respectfully disagree.

Jones et al is discussed supra. **McDevitt et al** teach a tumor antigen system conjugated via a chelator to the radioisotope, that results in greater internalization of the ^{225}Ac generator thereby helping to retain the daughters within the malignant cell and therefore leading to overall reduced radiotoxicity and enhanced potency (Page1540, 2nd Paragraph). In **McDevitt et al** the chelator is for the parent generator and further it discusses the retention of the daughters within the cell. **McDevitt et al** does not teach the use of chelates and diuretics for protection against nephrotoxicity. Although, **McDevitt et al** teach accumulation of the Bismuth-213 daughter in the kidneys as a result of the decay of the radioisotope, they do not report any nephrotoxicity associated with this accumulation.

The instant invention discusses the use of diuretics to clear the Francium daughter of Actinium 225. The amount of bismuth is reduced in the kidney because it is a daughter of francium and if francium drops, the bismuth will therefore too. In fact, **McDevitt et al** teach that although the prior art has reported that therapy with ^{225}Ac constructs might not be feasible because the constructs are unstable and because the radionuclide daughters present an untenable pharmacological problem, they report successful internalization and retention of their radioimmunoconjugate in the targeted tumors. Based on their results, one skilled in the art, would not be motivated to combine the teachings of **McDevitt et**

al with **Jones et al** and expect reasonable success. Accordingly, Applicants respectfully request that the rejection of Claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61 rejected under 35 U.S.C. 103(a) as being unpatentable over **McDevitt** et al (Science 2001; 294: 1537-1540) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113) be withdrawn.

Claims 5 and 53 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** et al (Science 2001; 294: 1537-1540) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of **Schilcher** et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60). Applicants respectfully traverse this rejection.

The Examiner states that the combination of **McDevitt et al** and **Jones et al** teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate similar to the instant invention, and an effective dose of a chelator. Further, the Examiner states that although the combination of **McDevitt et al**. and **Jones et al**. do not explicitly teach the administration of diuretics, this is taught by **Schilcher** et al for the preventitive cumulative nephrotoxicity associated with the administration of high dose cisplatin in various tumors. Applicants respectfully disagree.

McDevitt et al teach accumulation of daughter isotopes generated due to decay of the radoisotope in the kidney as evaluated by their assay of in vivo biodistribution. **McDevitt et al** does not teach any nephrotoxicity that compromises their ability to use the radioimmunoconjugate as an effective therapy. On the contrary, **McDevitt et al** teach that although the prior art has reported that therapy with ^{225}Ac constructs might not be feasible because the either stability issues with the radioimmunoconjugate or because the radionuclide daughters present an untenable pharmacological problem, the therapeutic efficacy of their radioimmunoconjugate is not affected by these issues. **Jones et al** disclose the evaluation of dithiol agents to reduce or prevent radiotoxicity of Lead-212 or Bismuth-212 alpha radioimmunotherapy. **Schilcher et al** teach

administration of diuretics for the preventitive cumulative nephrotoxicity associated with the administration of high dose cisplatin in various tumors. The metal poisoning of the kidney cells by ciplatin is fundamentally distinct and unrelated to the damage from the radiation associated or emitted by the acitinium daughters. The actinium daughters are only present in trace amounts in the kidney. Thus, the observed damage is not due to metal poisoning but due to the alpha radiation of the cells.

The instant invention addresses methods of protection from toxicity of alpha emitting elements during radioimmunotherapy and discloses the use of diuretics, competitive metal blockers, and chelators as a method of altering the pharmacokinetics of the radioimmunoconjugate, to enhance clearance of the daughter alpha particles generated during decay, and thus reduce nephrotoxicity. Since **McDevitt et al** do not teach any radiotoxicity associated with the administration of their radioimmunoconjugate, one of ordinary skill in the art would not at all be motivated to combine the teachings of **McDevitt**, **Jones** and **Schilcher** and expect reasonable success. Accordingly, the Applicant respectfully requests that the rejection of claims Claims 5 and 53 rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** et al (Science 2001; 294: 1537-1540) in further view of **Jones** et al (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of **Schilcher** et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60) be withdrawn.

Claims 4, 18, 26, 37, 44, and 53-54 are objected to as being dependent from a rejected independent claim. Applicant respectfully traverses this objection.

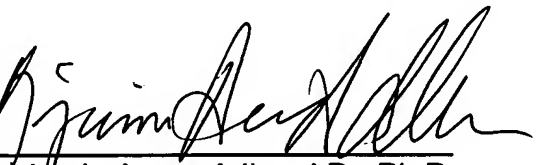
In view of the claim amendments and the discussions presented supra, claims 4, 18, 26, 37, 44, and 53-54 are no longer dependent from rejected independent claims. Accordingly, applicant respectfully requests that the objections be withdrawn.

Applicants have amended the oath of declaration to include the citizenship of the said inventors and have enclosed a copy herewith.

This is intended to be a complete response to the Office Action mailed April 6 2006. Applicants submit that claims 1-5, 7-8 and 10-17 are in condition for allowance and respectfully request that claims 1-5, 7-8 and 10-17 be passed to issuance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. In the absence of PTO Form 2038, please debit Deposit Account No. 07-1185 upon which the undersigned attorney is allowed to draw.

Respectfully submitted,

Date: Sept 6, 2006



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